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MECHANISMS OF ECCRINE ANIDROSIS

I. HIGH LEVEL BLOCKADE*

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Anidrosis, or lack of sweating, may be the result of no sweat being formed by the secretory gland or interference with the delivery of sweat to the skin surface. The problems of major clinical interest relate to disturbances in delivery and not to secretory inhibition, as after denervation or anticholinergic drugs.

Sweat retention may occur spontaneously in normal skin which has been profusely perspiring for days. If generalized, heat exchange is embarassed and the serious heat exhaustion syndrome, tropical anidrotic asthenia, may be precipitated. Localized anidrosis, however, may often be a covert condition without signs or symptoms except that the area remains dry after exercise or heat exposure. In predisposed persons the obstruction to the flow of sweat may lead to ductal distention and rupture, creating the clinically distinctive sweat retention rashes. It is the extravasation of sweat into the tissues which incites miliaria crystallina, miliaria rubra, and miliaria profunda according to whether the duct bursts respectively in its horny portion, intraepidermally or intradermally (1). Miliaria is, therefore, a two stage process; initially sweat blockade and secondly ductal rupture.

Actually there is firmer knowledge of the tissue abnormalities in miliaria than of the anidrotic state which precedes it and which is its necessary precursor. Indeed, the latter is clinically and histologically rather ordinary, notable for absence of activity, in contrast to the striking events which occur when sweat pours into, rather than onto, the skin. The debates and ambiguities in the literature concerning the nature of the block in the anidrotic state has prompted us to reexamine the problem experimentally.

Although miliarial reactions have been appreciated for more than a century to be somehow linked to sweat retention, firm experimental and histopathologic studies were pioneered by O'Brien (2, 3, 4, 5). This was all the more remarkable since the finer details of structure of the terminal portion of the duct in the epidermis and horny layer, were not known. The concept of the epidermal sweat duct unit was to be developed later. O'Brien postulated that closure of a 'keratin ring' forming the wall of the sweat pore was responsible for the anidrotic state. Poral closure was not further defined anatomically; a physical plug was apparently not seen. O'Brien first thought that lipoid depletion was responsible for poral closure; later maceration and bacterial colonization were suggested as initiating events. In miliaria rubra, on the other hand, the sweat orifices were clearly obstructed by parakeratotic horny masses. Sulzberger emphasized the presence of such plugs in chronic skin lesions (6) and in miliaria rubra (7). In his view, these horny plugs were the primary cause of sweat retention. In a series of classic studies, Shelley and his coworkers (8, 9, 10, 11) induced miliaria experimentally in a variety of ways ranging from simple wet dressings to physical modalities (iontophoresis, heat, cold) and chemical agents (phenol, chloroform and aluminum chloride). Extensive histopathologic examination of miliarial lesions convinced these workers that hyperkeratotic and parakeratotic obstructive masses were responsible for sweat retention. Usually tissues were examined after miliaria had been evoked by heat exposure, some days after the original insults. The preceding anidrotic state, when the skin was still clinically normal, was not thoroughly studied. Cormia and Kuykendall (12) studying chronic dermatoses, observed casts of PAS positive, dia-

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stase resistant material within the parakeratotically plugged sweat ducts. They speculated that this might be the primary cause of ductal obstruction. The demonstration of occlusive plugs in miliaria and in chronic dermatoses was so convincing that it no longer seemed necessary to examine other possibilities in the causation of anidrosis. Indeed, the important distinction between simple sweat retention and miliaria became obscure.

Nonetheless, two separate lines of investigation re-opened the question of the nature of the obstruction in the primary stage of anidrosis. Hambrick and Blank (13) prepared whole mounts of skin affected by miliaria crystalline and were unable with the most meticulous technic of examination to demonstrate a physical plug of any kind. In addition, Dobson and Lobitz, (14) in their study of miliaria induced by iontophoresis, noted that parakeratotic plugs were part of the healing pattern after and not before rupture of the duct. They deduced that keratotic plugging was a secondary response to injury. There was agreement, however, that once such plugs had formed, as in miliaria rubra, sweat delivery would be effectively blocked, thus perpetuating the disorder. In searching for a primary cause of closure, these workers proposed that the PAS positive, diastase resistant casts, seen also by Cormia and Kuykendall, (12) were probably the initial obstruction. Perhaps their most fundamental observation was that the PAS positive, diastase resistant granules composing the cast were probably derived from the cells of the secretory coil of the gland (15). These granules entered the lumen and tended to coat the surface along the entire length of the duct. An excessive accumulation could form a plug. In the midst of this uncertainty, Sulzberger (16) theorized that alterations in the electrophysiologic potential along the duct might offer a functional interference with sweat delivery, thus coming full circle to O'Brien's cautious, functional identification of 'poral closure'.

We have focused our attention on the characteristics of anidrosis, ignoring for the time being the sequelae of miliaria and its obvious histopathologic changes. Although we used many of the experimental technics, of Shelley and his co-workers (8, 9, 10, 11) we examined the sites shortly after the onset of anidrosis, attempting thereby to eliminate changes secondary to ductal rupture.

We discuss in this paper that type of anidrosis, regardless of cause, which stems from an obstruction, whether physical or functional, in the terminal portion of the eccrine duct located in the horny layer. High level blockade is the term used to specify the superficial situation of the occlusion.

METHODS

1. Estimation of Sweat Function

Thermal initiation of perspiration was carried out by placing the subjects in environment chambers at 100° F and 90% relative humidity. The duration of sweating, 30 minutes, was timed from the onset of visible perspiration. Sweat droplets were observed by painting a starch-castor oil mixture over the skin, without the use of iodine (17). This procedure allows estimation of the activity and density of functioning sweat glands even in the presence of serum, and avoids possible inhibitory effects of the alcoholic iodine used in the Wada technic (18). The sweat appears as distinct white droplets beneath the transparent film of castor oil. All experimental maneuvers and biopsies were performed on the volar forearms. The subjects were healthy adult males except some with chronic dermatoses.

2. Removal of Stratum Corneum

The horny layer was stripped to the glistening layer with Scotch Tape®, in order to test for the presence of obstructions in the stratum corneum portion of the terminal eccrine duct. Physical removal of the horny layer in such a case would necessarily be followed by sweating on sites which were anidrotic beforehand.

3. Iontophoresis of Methylene Blue

We previously analyzed the well known punctate pore pattern which exactly locates the eccrine ducts following the iontophoresis of methylene blue into normal skin (19). The pattern results from the dye traversing the eccrine duct and diffusing into the surrounding epidermal tissue. This can only happen if there is no poral obstruction and is thus a test of patency. Furthermore, for unknown reasons, the glands must be actively secreting, a test of functioning. Iontophoresis was performed with a 0.1% methylene blue solution for five minutes at a current density of 0.5–0.75 milliamperes per cm^2.

4. Histology

Excisional biopsy specimens were obtained from anidrotic and from control sites prior to thermal stress, and again following 30 minutes of active perspiration. This was done to judge anatomic and histochemical changes in the anidrotic sites subsequent to the forced sweating. Tissues fixed in 10% neutral buffered formalin were serially sectioned and alternately stained with hematoxylin and eosin and PAS, with and without diastase

digestion. Areas which had been denuded of stratum corneum by the stripping procedure were not included in the histologic material since the technique itself alters the test site.

5. Experimental Anidrosis

Distilled water, 10% formalin, 5% trichloracetic acid or 10% chromium sulfate solutions were applied to volar forearms of the subjects for 18 hours, overnight. Thoroughly wetted, two inch square gauze pads were kept beneath an impervious plastic film of Saran Wrap®* and impermeable adhesive Clear Tape®†. Thirty subjects were studied using all four test solutions as described. Such treatment uniformly produced anidrosis, in the occluded sites, which persisted for an hour in the simple water patch, and for several days to a week following application of the protein precipitating solutions.

RESULTS

I. Chronic Dermatoses

The lesions of two subjects with atopic dermatitis and two with psoriasis were completely anidrotic following the thermal stress, in agreement with all previous observations. Adjacent normal skin, however, sweated profusely. After stripping, numerous sweat droplets appeared in the previously anidrotic sites. (Fig. 1) When compared to the normal sweat pattern, it was evident that this represented only a partial, though significant return of perspiration. It seems reasonable to conclude that removal of the horny layer carried away, to a considerable degree, some physical obstruction in the superficial portion of the ducts. We agree with Suskind, however, that the inflammatory process itself might partially interfere with secretion or resorption of sweat (20).

The histopathologic findings after thermal stress supported the role of the parakeratotic masses as physical obstructions. First of all, the intraepidermal duct was widely dilated, presumably from damming back of fluid. This distention was sometimes great enough to dilate the deeper dermal portions of the duct as well. (Fig. 2) In fixed specimens, wide dilation, not mere visualization of the lumen, is the only reliable sign. Below the parakeratotic mass, a cast of PAS positive, diastase resistant material accumulated. These casts were also noted by Cormia and Kuykendall (12) when secretion was stimulated by intradermal injection of methacholine into psoriatic skin.

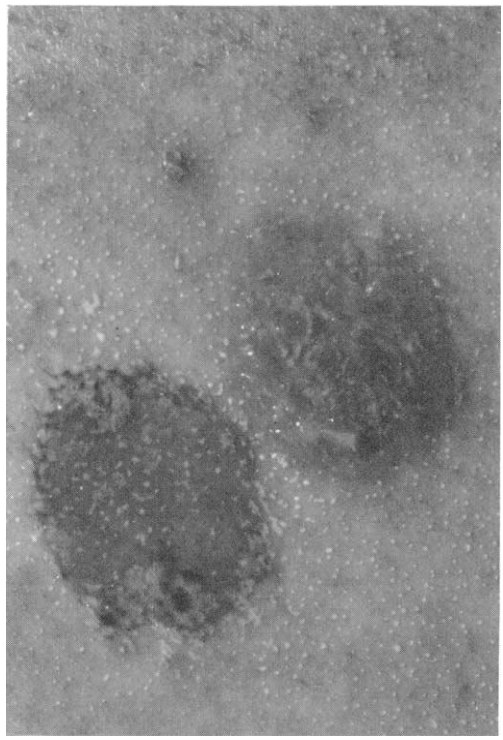

FIG. 1. Reversal of anidrosis in psoriasis. The lower left lesion has been stripped with Scotch Tape® to remove the stratum corneum, and the entire area coated with a starch-castor oil film. Following thermal stimulation, sweat droplets, seen as white puncta, are present in the normal skin and the stripped lesion; the undisturbed plaque remains anidrotic. Note that there is no halo of anidrosis about the dermatitic area, but that droplets of sweat appear right up to the margin of the lesion.

Formisano and Lobitz (15) have presented strong evidence that this material arises from the secretory coils and is swept out into the duct into the flow of sweat. It is not at all surprising that it should become impacted below the point of physical obstruction. Finally, after sweating, glycogen disappeared from the cells of the ducts and coils as it does in normal skin suggesting that the obstruction does not result in total shut-down of sweat secretion. This is in further support of the observation that newly formed perspiration dilates the blocked ducts, and reinforces the notion that the PAS positive diastase resistant material, which is actively secreted, accumulates as a result of the obstruction.

An important reason for the failure of strip-

* Dow Chemical Co., Midland, Mich.
† Johnson & Johnson, New Brunswick, N. J.

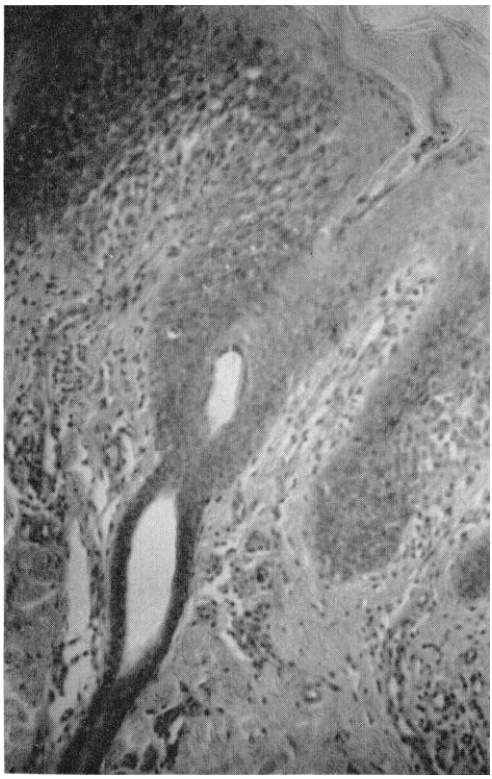

FIG. 2. Post-sweating ductal dilatation in atopic dermatitis. This degree of distention is not present in specimens taken before the thermal stress or on normal skin after sweating. Also note that the dilatation extends deeply, well into the dermis. The high intraepidermal and horny layer portions of the duct may be seen to contain the PAS positive, diastase-resistant material which accumulates behind the obstructed eccrine ostia. (PAS, original magnification × 190)

ping to restore patency to all the ducts was afforded by the histologic observation that the parakeratotic plugs were not always superficially situated in the orifices. Often they extended down into the intraepidermal portion, well beyond reach of Scotch Tape®. (Fig. 3)

II. Hydration Anidrosis

Before studying the mechanisms of sweat suppression by various chemicals, it is well to consider what water alone will do to the skin. Randall and Peiss (21) clearly demonstrated that absorption of water by the stratum corneum would cause anidrosis so long as the horny tissue remained swollen. By immersing the hands in water, they achieved anidrosis within 30 to 60 minutes with gradual return of sweating upon air drying within a similar time period. In hypertonic saline solutions, immersion failed to produce suppression because water absorption and swelling was prevented. As both Shelley and O'Brien before us, we produced anidrosis by holding moistened pads occlusively against the skin for a number of days. In most subjects, the anidrosis persists for a surprisingly long time, well beyond the few hours required for the horny layer to dry out. There may be complete anidrosis for a couple of days; thereafter an increasing number of ducts deliver sweat although full return does not usually occur for a week. Occasionally, complete restoration may require two weeks. Nonetheless, these hydration induced anidrotic sites responded immediately to Scotch Tape® stripping. Resumption of a nearly normal sweat

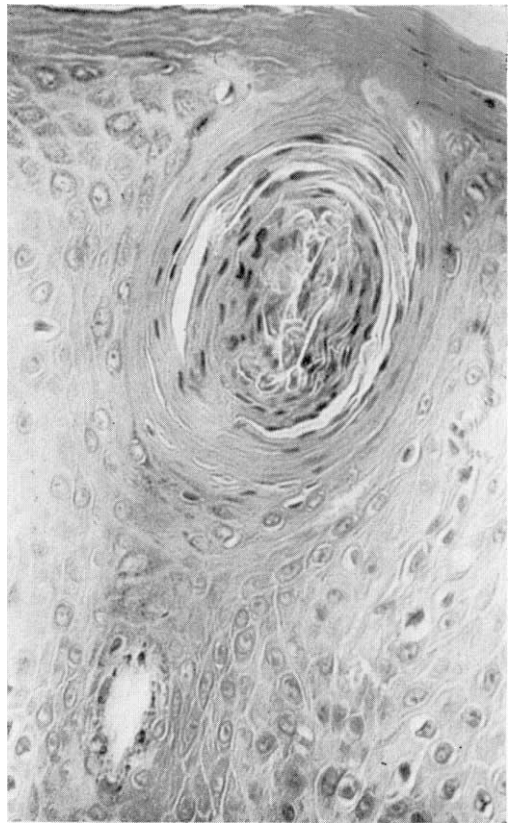

FIG. 3. Parakeratotic plugging of eccrine duct in atopic dermatitis. Note that the deeper epidermal portion of the duct is slightly dilated in this specimen, taken before the patient was exposed to heat. This is followed by great distention after the sweating stimulus. H & E original magnification × 167

pattern occurred instantly following removal of the stratum corneum. This could be demonstrated at any stage of the anidrosis.

When impermeable adhesive tapes or plastic wrapping (Saran Wrap®) alone are used to occlude the skin surface for longer periods of time, such as six days, all subjects develop a complete anidrosis. If allowed to resolve spontaneously, restoration of normal sweating takes seven to ten days. Marples, in our laboratory, has shown that this effect is intimately connected with the great proliferation of resident bacterial flora under the plastic sheet (22). Pretreatment with topical antibacterial agents reduces, and may prevent, the development of anidrosis. Again, the sweat suppression is considerably reversed by stripping off the stratum corneum.

Although some physical obstruction was carefully searched for in our histologic material, the terminal portion of the eccrine ducts appeared perfectly normal. While O'Brien reported bacteria in the superficial coils (4), even this finding has been rare in Marples' studies. Ductal distention and disappearance of glycogen after sweating were characteristic findings in our material. These were regarded as evidences of active sweat secretion. Marples has regularly produced miliaria in his studies by repeated thermal stressing, further confirming ductal occlusion. It must be emphasized that obstruction may be present without detectable anatomic plugging. Prior studies by Hambrick and Blank (13) have amply demonstrated obstructive masses are not to be found in miliaria crystallina.

III. Anidrosis by Protein Denaturants

The diverse experimental modalities employed by Shelley and co-workers (8, 9, 10, 11) truly emphasize that many types of damage may create proper conditions for the development of miliaria. We also have frequently observed that irritants applied in the course of patch testing, *e.g.* croton oil, nickel and mercury salts, etc., will produce anidrosis. Chemical irritation is a difficult system to study since the sweat retention is complicated by extensive epidermal damage—edema, inflammation, etc. To simplify this type of experimental anidrosis we sought to produce the slightest possible injury to the very superficial portion of the horny layer. Accordingly, either 5% trichloracetic acid, 10% formalin or 10% chromium sulfate were applied under occlusive patches. The skin remained clinically normal.

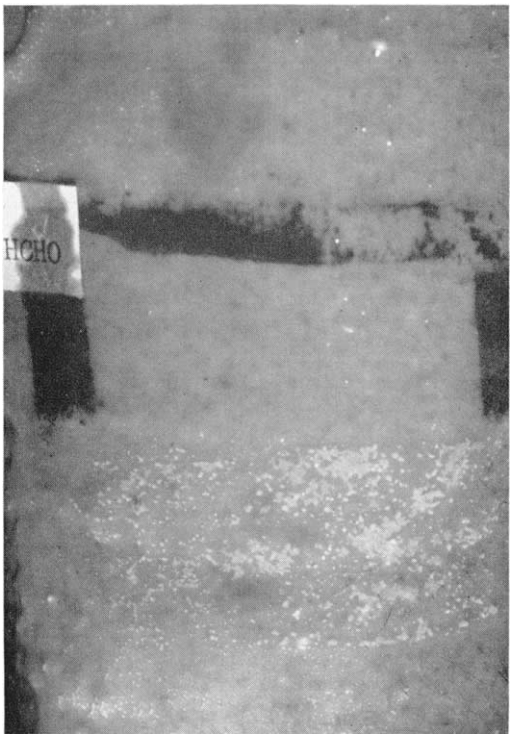

FIG. 4. Reversal of protein denaturant anidrosis. Treatment with 10% formalin under occlusion has rendered the test site anidrotic. Subsequent stripping of the lower half of the area however reverses this inhibition. The white puncta of developing sweat droplets, seen through the starch-castor oil film, are present only where the stratum corneum was removed and in untreated skin on the periphery.

Removal of the stratum corneum by Scotch Tape® stripping, at any time during the subsequent anidrosis produced by the protein precipitants, brought about a return of sweating. Droplets of perspiration filled the denuded test area, in this case with complete restoration of a normal pattern. (Fig. 4) This was dramatic evidence of superficial obstruction. That there was a true block was indicated by the inability to produce a pore pattern with methylene blue iontophoresis. The duct and periductal tissues were not stained because the dye simply could not enter the eccrine ostia, preventing formation of the typical blue punctate pattern on the skin. Histologic examination verified the clinical impression that there was little or no inflamma-

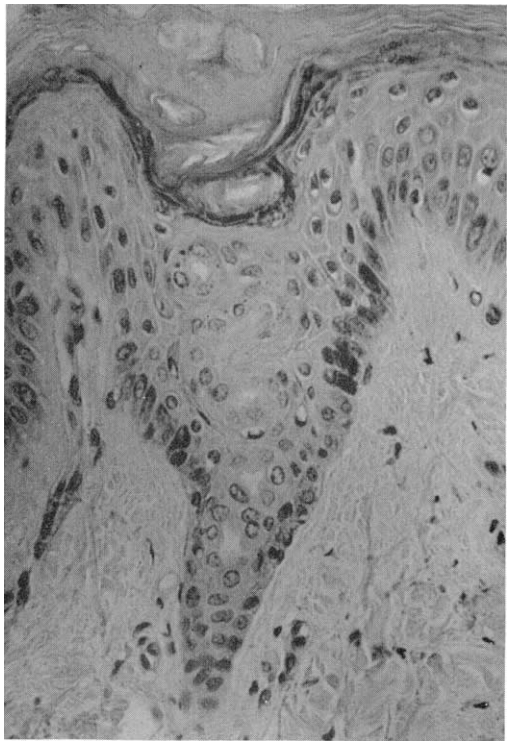

FIG. 5. Plugging of the superficial portion of the eccrine duct following treatment with 5% trichloracetic acid. These amorphous intraluminal masses are not found in normal skin and are not PAS positive. It is apparent why removal of the stratum corneum reverses the anidrosis produced by the protein denaturants. (H & E—original magnification × 60)

tion, nor were any important toxic changes seen in the epidermis. In the H and E sections, the significant finding, indeed, the hallmark of this type of anidrosis, was the presence of an amorphous intraluminal cast within the uppermost spirals of the eccrine duct. (Fig. 5) This material was not PAS positive. After the usual heat stress, both the intraepidermal and upper dermal portions of the eccrine ducts were widely dilated. Most noteworthy was the formation of the PAS positive, diastase resistant granular material under the original occluding mass, similar to that which occurred beneath the parakeratotic plugs in the chronic dermatoses. It is clear that this substance accumulates after sweating, whenever the duct is occluded. (Fig. 6) Disappearance of glycogen from the secretory cells following the sojourn in the sweat chamber provided additional evidence that glandular activity continues in the face of high obstruction, and is responsible for the subsequent dilatation.

DISCUSSION

Research activity in eccrine miliaria since O'Brien's signal contributions has greatly increased our knowledge of both normal and abnormal sweat gland function. Nonetheless serious informational gaps and misunderstandings have remained. There is considerable confusion concerning the nature of the obstruction in the anidrotic state. Some of this difficulty stems from a failure to distinguish between the causes of anidrosis and the effects of the miliarial reactions. Obstructive plugs are a secondary event following upon the repair of ruptured ducts. Repeated rupture intensifies the plugs and sustains the occlusion. Easy generalizations have evolved from these observations and, as a

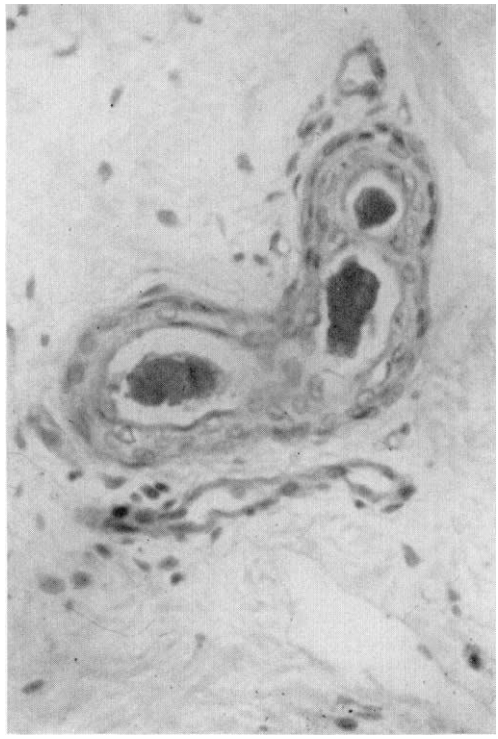

FIG. 6. Dilation of the deep dermal eccrine ducts and accumulation of PAS positive, diastase-resistant material on formalin treated anidrotic site, following thermal stress. Very small amounts of this intraluminal matter are found behind superficial plugs before sweating. The heat stimulus causes relatively large amounts to be seen along the entire length of the eccine ducts. (PAS, original magnification × 167)

result, too much emphasis has been accorded plugging as *the* cause for sweat retention, despite the fact that such anatomic obstructions have not been observed in the pre-miliarial state, or for that matter, in the highly superficial miliaria crystallina. It is the prerequisite anidrosis, that which precedes ductal rupture, that has been largely ignored. Moreover, it must be remembered that all anidrosis does not invariably evolve into miliaria; on the contrary, only a relatively small number of susceptible individuals do develop the syndromes under repeated or prolonged conditions of thermal stress. Our studies have shown that there are several general mechanisms, distinct from direct glandular suppression or post-miliarial blockade, which operate to inhibit sweating. In this paper we have been solely concerned with occlusion which occurs in the superficial poral portion of the eccrine duct.

A diagnosis of high level anidrotic blockade requires the following:

(1) Removal of the stratum corneum relieves the obstruction and allows significant sweating on previously anidrotic skin. In the anidrosis of certain chronic dermatoses such as psoriasis and atopic dermatitis, however, this may not be completely successful, partially because of the presence of some deep parakeratotic plugs which the Scotch Tape® stripping fails to remove. Additionally, other mechanisms may disrupt secretory activity or ductal transport since the skin is the site of intense inflammation.

(2) High level blockade prevents iontophoresis of methylene blue into the sweat ducts. It is impossible to obtain the distinctive blue puncta which locate the eccrine ducts. The dye which normally traverses the duct and diffuses into the periductal tissues is denied access by the block. In addition pore patterns cannot be produced when secretion is prevented by anti-cholinergic agents even when ducts are patent. A typical pattern verifies the absence of obstruction and the presence of secretory activity. The stripping technic quickly establishes activity, and histologic verification further demonstrates this.

(3) Distention of the eccrine duct after forced sweating. Some care in judgment is required for this observation since in the past too many barely visible lumina have been interpreted as dilated ducts, when in fact, the necessary broad and gaping structures were lacking. When active secretion exceeds ductal reabsorption, sweating into the blocked system necessarily produces dilatation. Shelley concluded that back pressure in obstructed ducts brought about secretory shut-down (23). He judged this from the persistence of glycogen after sweating. Glycogenolysis did occur however, when the duct ruptured; that is to say, in miliaria but not in simple anidrosis.

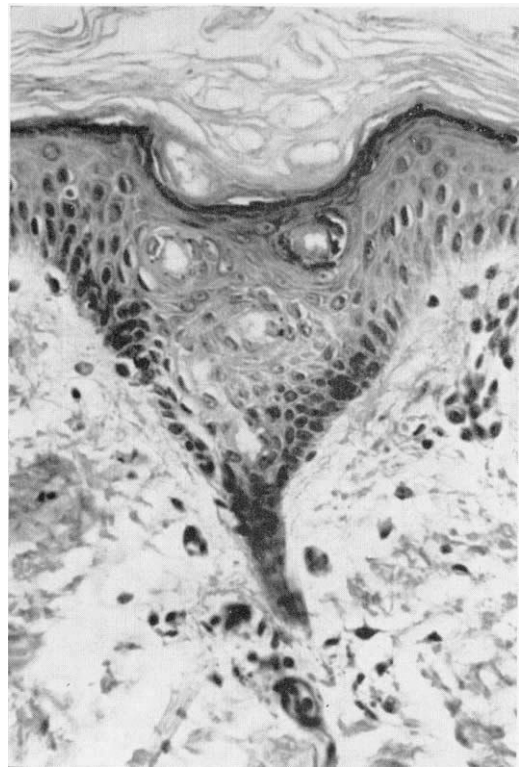

FIG. 7. Normal skin. The terminal coils of this patent duct wind through a depression or 'beaker' which is filled with a weave of horny material. This appearance is perfectly normal, although pictures similar to this have been published to illustrate horny obstruction or plugs. (H & E, original magnification × 152)

Our results are discordant. After sweating, glycogen readily disappears from the secretory coil of blocked ducts regardless of the nature of the obstruction. We take this to mean that secretory activity does not cease entirely in the anidrotic state. Both the dilatation and the PAS positive casts indicate that complete shut-down has not occurred. With regard to the fate of fluid secreted into a blocked duct, one need only postulate its resorption in the duct, a

function which almost certainly occurs under physiologic conditions. Casts may form throughout the length of the duct since the material is denied its usual exit onto the skin surface. We have no evidence that this intraluminal material is a primary cause of obstruction. On the contrary, it signifies the existence of a prior obstruction.

It is well to emphasize that the plugs produced experimentally by the protein precipitants are not to be confused with the casts mentioned above. They tend to be amorphous rather than granular, are exclusively located in the uppermost portion of the horny layer duct, and do not take the PAS stain.

Lack of detailed knowledge of the normal anatomy of the sweat duct orifice has been the source of some faulty interpretations. Previous workers have presented pictures of perfectly normal orifices which they interpret to be blocked by a horny mass. Hambrick and Blank's whole mount preparations adequately clarify this problem. By surface inspection, even with magnification, one cannot locate the sweat pores anywhere except on the palms and soles. In cross sections however, the terminal portion of the duct winds its way through a small 'beaker' or cup-like depression which contains a mass of horny material. These horn filled beakers are not obstructions; neither are they equatable with O'Brien's "keratin ring." The sweat pore is lined with its own intrinsic horny lamellae produced by keratinization of the double layer of cells encircling the ductal lumen. The horny material in the 'beaker' is extrinsic to the pore. (Fig. 7)

When the criteria for demonstrating high level blockade are satisfied, the question of the nature of the obstruction must then be answered. While actual plugs may be visualized in chronic dermatoses and after application of protein precipitants, no physical obstruction can be identified in hydration anidrosis. Swelling of keratinized tissue is an adequate explanation for the transient anidrosis produced by immersion in water for a few hours or less. This anidrosis ceases as soon as the horny layer dries out. As early as 1893, Pollitzer proposed that the imbibition of water and swelling of the stratum corneum could produce miliaria (24). Actual visualization of poral closure with hydration anidrosis of the palms has been achieved by Sarkany *et al* (25) using plastic replication technic. This confirms anatomically what has been shown functionally by Randall and Peiss (20).

Nonetheless, simple swelling is not an accepted explanation for the persistant anidrosis after several days of occlusion under impermeable dressings. Some subtle apparently functional change occurs which sustains the anidrosis for a week or more after the horny layer is allowed to dry out. High level blockade by "poral closure", an admirable term coined by O'Brien which covers all types of occlusion, anatomical and functional, is but one mechanism of producing eccrine anidrosis.

SUMMARY

The cause of anidrosis of the chronic dermatoses, hydration, and that produced experimentally by protein precipitants is superficial obstruction of the eccrine duct. In each instance, return of sweating in the anidrotic area is effected simply by removal of the stratum corneum with Scotch Tape® stripping. The histologic picture common to this type of anidrosis is ductal dilatation following an adequate sweat stress. The presence of an obstruction, whether functional or anatomic, is confirmed by the inability to achieve a methylene blue pore pattern.

Parakeratotic plugging of the eccrine ostia is primarily responsible for the obstruction in the spontaneous dermatoses, while actual intraluminal casts are produced chemically by the protein denaturants, high within the stratum corneum portion of the eccrine duct. The PAS positive, diastase resistant casts regularly found in blocked ducts are secondary to the obstruction and are not a primary cause. No adequate explanation has been found for the persistent anidrosis after occlusion of the skin with impermeable plastic dressings.

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